

## **REMARKS**

Claims 26-75 are pending. Claims 26, 31, 35, 38, 43, 46, 53 and 55 have been amended. Claims 56-75 have been added. Support for new claims 56, 61, 66 and 71 can be found in the specification at page 10, line 16 to page 11, line 4. Support for new claims 57, 62, 67 and 72 can be found in the Preliminary Amendment filed July 18, 2003 at page 2. Support for new claims 58, 63, 68 and 73 can be found in the specification at page 9, line 25 to page 10, line 15. Support for new claims 59, 64, 69 and 74 can be found in the specification at page 11, lines 5-7. Support for new claims 60, 65, 70 and 75 can be found in the specification at page 17, lines 21-25. Support for amended claims 26, 35 and 43 can be found in the specification at page 10, line 16 to page 11, line 4. Claims 31, 38 and 46 have been amended to correct a duplication of the term "amphetamine." Claims 53 and 55 have been amended to correct their dependency from canceled claim 24 to claims 52 and 54, respectively.

Reconsideration of this application is respectfully requested.

### **The rejection of claims 53 and 55 under 35 U.S.C. § 112, second paragraph**

Claim 53 has been amended to depend from claim 52 and claim 55 has been amended to depend from claim 54. Accordingly, this rejection should be withdrawn.

### **The rejection of claims 26-55 under 35 U.S.C. § 103(a)**

Claims 26-55 have been rejected as being obvious over WO 01/26623 ("Horrobin"). Horrobin discloses the use of a selective norepinephrine reuptake inhibitor together with phenylalanine or tyrosine for the treatment of chronic fatigue syndrome ("CFS"), fibromyalgia syndrome ("FMS") and symptoms associated therewith, including pain. The Examiner contends that it would have been obvious to one of ordinary skill in the art to use SNRIs to treat FMS, CFS and pain in view of Horrobin.

As amended, independent claims 26, 35 and 43, and the claims dependent therefrom, are not obvious because Horrobin teaches away from the use of noradrenaline reuptake inhibitors (or noradrenaline and serotonin reuptake inhibitors) without co-administration of phenylalanine or tyrosine. Horrobin discloses the case history of a patient with CFS, FMS and irritable bowel Application Serial No. 10/623,431

syndrome (“IBS”) who was not effectively treated with various drugs including “serotonin reuptake inhibiting and noradrenaline reuptake inhibiting antidepressants” (Horrobin, page 8). The patient only improved following administration of lofepramine, a selective noradrenaline reuptake inhibitor, in combination with L-phenylalanine. Thus, the patient only improved when the selective noradrenaline reuptake inhibitor was co-administered with a neurotransmitter precursor (i.e., L-phenylalanine). According to Horrobin, serotonin reuptake inhibitors or noradrenaline reuptake inhibitors alone are ineffective.

Further, the dependent claims directed to adjunctive treatment with additional compounds, specific dosages, and dosage formulations would not have been obvious because Horrobin does not disclose or suggest that a SNRI that is not co-administered with a neurotransmitter precursor such as phenylalanine, tyrosine or tryptophan would be effective in combination with any other compound, at any specific dosage, or in any specific formulation. In fact, Horrobin suggests that any treatment, other than a selective norepinephrine reuptake inhibitor in combination with a neurotransmitter precursor such as phenylalanine, tyrosine or tryptophan would almost certainly fail. The patient with FMS, CFS and IBS “was given almost all conceivable treatments over the years, including many types of non-steroidal anti-inflammatory drugs, both tricyclic and serotonin reuptake inhibiting and noradrenaline reuptake inhibiting antidepressants, and even steroids. Some of these treatments produced transient effects but these never lasted” (Horrobin, page 8). Thus, there was no reasonable expectation from the Horrobin teachings that a SNRI in combination with any compound that is not a neurotransmitter precursor such as phenylalanine, tyrosine or tryptophan in any dosage or in any dosage formulation would have been successful for the treatment of pain, FMS, CFS, or symptoms associated therewith.

Moreover, the Examiner contends that claims 50-55 would have been obvious because inclusion of a package insert is mandated by 21 CFR 201.57 and unit dose packaging is routine in the pharmaceutical art. Amended claims 50-55 would not have been obvious because there would have been no motivation to include a package insert teaching a method for treatment that had no reasonable expectation of success.

In view of the foregoing, this rejection should be withdrawn.

**The rejection of claims 35-42 under 35 U.S.C. § 103(a)**

Application Serial No. 10/623,431

Claims 35-42 have been rejected as obvious over Moreau et al. (DRUGU AN 1992-39596) (“Moreau”) in view of Woerz zum Thema (DRUGU AN 1983-01770) (“Woerz”).

According to the Examiner, Moreau discloses the use of antidepressants to treat pain and Woerz discloses that milnacipran, an SNRI, is an antidepressant agent. Thus, the Examiner contends, it would have been obvious to use milnacipran to treat pain, and the dependent claims, which recite dosage regimens and dosages, are obvious because these were matters of routine optimization. Dependent claims to SNRIs administered adjunctively with another active agent are obvious according to the Examiner because Woerz discloses that neuroleptics and opiates are used to treat pain.

This rejection is respectfully traversed. Moreau does not disclose or suggest the use of antidepressants to treat pain nor does it disclose that milnacipran is an antidepressant agent. Moreau discloses the electrophysiological effects and clinical tolerance of intravenous milnacipran compared to imipramine-like antidepressant agents. Woerz discloses the use of drugs, including “antidepressants, e.g. doxepine, amitryptyline, imipramine and clomipramine” for the treatment of cancer pain. All of the exemplified antidepressants are tricyclic antidepressants and not SNRIs. Thus, Moreau and Woerz do not disclose or suggest the use of an SNRI (e.g., milnacipran) for the treatment of pain. Thus, the rejection of claims 35-42 under 35 U.S.C. §103(a) should be withdrawn.

#### **The rejection of claims 50-55 under 35 U.S.C. § 103(a)**

Claims 50-55 have been rejected as obvious over EMBASE AN 1998129084 (“‘084”) or EMBASE AN 90228858 (“‘858”). According to the Examiner, ‘084 discloses the use of milnacipran in ambulatory and hospital settings, and ‘858 discloses the use of milnacipran in hospitalized patients. According to the Examiner, claims 50, 52 and 54, which are directed to a kit with instructions, would have been obvious in light of these references because a package insert teaching a method of use is mandated by 21 CFR 201.57. Dependent claims 51, 53, 55 recite unit dose packaging. Such packaging is routine in the pharmaceutical art, according to the Examiner, and therefore would be obvious, especially in an institutionalized setting such as disclosed in ‘084 and ‘858.

It would not have been obvious to assemble a kit including an SNRI with instructions for treating CFS, FMS or pain because, in accordance with amended claims 50-55 and the arguments above, methods for treating these conditions with an SNRI are nonobvious. Thus, this rejection should be withdrawn.

**The provisional rejection of claims 26-55 for double-patenting**

Applicant acknowledges that claims 26-42 have been provisionally rejected for obviousness-type double-patenting over claims 1-7 of U.S. Patent No. 6,602,911; claims 35-49 have been provisionally rejected for obviousness-type double-patenting over claims 1-5 of U.S. Patent No. 6,635,675; and claims 26-55 have been provisionally rejected for obviousness-type double-patenting over claims 10-16 and 24-25 of co-pending Application No. 10/623,378. Since this is a provisional rejection, Applicants defer addressing the rejection until allowable subject matter has been identified in this application. If this rejection remains at that time, Applicants will address the rejection.

**The Information Disclosure Statement**

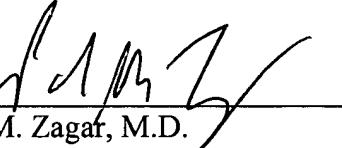
According to the Examiner, several references, which were included in an Information Disclosure Statement were not considered because copies were not present in the file of the parent application. A Supplemental Information Disclosure Statement, form PTO/SB/08 and copies of references EP 0759299, FR 2752732, WO 97/35584, WO 99/59593, WO 00/32178, WO 02/053140, Dwight, Goodnick, Ninan, Nutt & Johnson, and Rao are enclosed. Applicant respectfully requests that the references be considered and made of record in this application. We have not identified a reference corresponding to MEDLINE, et al., "Treatment of chronic fatigue syndrome with sibutramine ..." PCT Int'l Appl. 14 (09/28/2000).

**Conclusion**

No new matter has been added by these amendments. In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,

By   
Paul M. Zagar, M.D.  
Registration No.: 52,392  
DARBY & DARBY P.C.  
P.O. Box 5257  
New York, New York 10150-5257  
(212) 527-7700  
(212) 753-6237 (Fax)  
Attorneys/Agents For Applicant

Dated: December 29, 2004